It is, therefore, suggested that the presence of glucose in the blood stream is the factor responsible for the prevention of methemoglobin formation so often noted experimentally in some animals.

It is also suggested that injections of glucose in saline be used clinically in cases where methemoglobin is present, either as a result of poisoning by anilin dyes, nitrites, or any other methemoglobin producing substances, or where factors exist to produce this condition clinically.

107 Woodmont Avenue.

MATILDA M. BROOKS,
Berkeley.

ISO-ANAPHYLAXIS †

The intuitively assumed non-toxicity of normal, adult human serum is not justified by clinical experience. This is indicated by a half-dozen reports of shock-like conditions following the injection of adult human serum into children.[1] This iso-allergic reaction cannot be explained as a result of physical or chemical denaturation of the injected human serum. There is at least one clinical report of equally serious serum disease following the injection of absolutely fresh, non-heated and demonstrably sterile normal human serum, to which no antiseptic of chemical preservative had been added.[2]

The possibility of iso-allergic shock, due to the injection of serum of the same animal species but of a different blood group, is still untested in laboratory research. This is due to the comparatively recent date of the discovery of different blood groups in animals.[3] The well-confirmed production of group diagnostic iso-agglutinins, iso-hemolysins, and isoprecipitins, however, strongly suggests its future laboratory demonstration.

The possibility of iso-anaphylaxis, due to the use of serums of different age groups, is also largely untested in laboratory research. This is due to the comparatively recent discovery that the animal body is not static in its humoral or cellular specificities. While the available data are inadequate for a detailed theory, there is ample evidence of an hereditary (or environmentally induced) maturation cycle in laboratory animals, with the appearance of numerous previously undemonstrable specificity factors during the pre-adolescent or early adolescent periods.[4] It is alleged, for example, that the injection of adult rabbit serum into immature rabbits leads to the production of adult diagnostic isoprecipitins, by means of which the serological maturity of a rabbit can be approximately diagnosed.[5]

The possibility of pseudo-isoanaphylaxis from circulating food proteins in adult human serum is also, thus far, inadequately tested. This is due to the relatively recent demonstration that the normal gastro-intestinal mucosa is an inefficient barrier against the absorption of gastro-intestinal colloids. Quantitatively measurable amounts of egg protein, for example, are demonstrable in the normal human circulation within twenty minutes after swallowing a raw egg.[6] Pollen proteins are absorbed through the normal nasal mucosa with equal ease.[7]

There is rapidly increasing evidence that such absorbed (or parenterally injected) alien proteins are not promptly destroyed or eliminated from normal animal tissues. Certain recent theorists, for example, have assumed that these absorbed (or injected) alien proteins are semi-permanently retained in the animal body, and there synthesized into semi-alien antibodies.[8] It is definitely known, however, that blood transfusion from a horse-protein injected dog into a horse-protein hypersensitive recipient will throw the recipient into acute anaphylactic shock even as late as six days

† The *Journal of the American Medical Association*, in the July 21, 1934, issue, page 192, prints a current comment article on a related topic which is here reprinted. It is as follows:

"*Sudden Death After Injection of Human Serum.*—While normal human serum is presumably the least toxic therapeutic agent that can be used in attempting passive immunization of children, the opinion that such serum can be injected without danger into children is not justified by clinical experience. European clinicians [1] report that the administration of human serum to children under fourteen years of age is sometimes followed by severe or even serious serum disease in approximately three per cent of the cases. The term "auto-anaphylaxis" has been suggested as a descriptive title for this type of serum shock.[2] The term "iso-anaphylaxis," recently suggested,[3] is, however, more nearly in accord with recent immunologic nomenclature. Assuming that the adult human serums are selected and prepared by competent clinicians and laboratory technicians so as to rule out all dangers from the selection of pathologic serums or from subsequent bacterial contamination, the most obvious explanation of iso-anaphylactic toxicity would be that it is due to physical or chemical denaturation of normal serum proteins. This is probably not the full explanation, however, for investigators [4] report equally serious serum disease following the injection of absolutely fresh, nonheated and demonstrably sterile normal human serum, to which antiseptic or chemical preservatives had not been added. A second obvious explanation would be to assume that the iso-allergic toxicity is due to circulating food proteins [5] or to other circulating environmental allergins,[6] to which the children receiving the serum had a hereditary or acquired specific sensitivity. If this is so, one evident precaution would be to withdraw no serum from donors until at least eight hours had elapsed after the last protein meal. Less plausible explanations are based on the still hypothetical differences in tissue and serum specificity between young children and adults,[7] on the possibility of allergic shock due to the use of adult serums of an alien blood group and on the conceived possibility of "reversed anaphylaxis." [8] The latter would be due to the presence of specific or nonspecific "antibodies" in many normal adult circulations [9] against antigens conceivably present in certain children. Thus far, but one case of iso-allergic serum disease has been reported in American literature.[10] There are several still unreported cases, however, in the recent California experience. No fatality is as yet on record directly attributable to iso-anaphylactic shock." [11]

1 Netter, A.: Compt. rend. Soc. de biol., 78:505, 1915.

2 Nelli, A. R.: Rinasc. med. 7:523 (Nov. 1), 1930.

3 Manwaring, W. H.: Calif. and West. Med., to be published.

4 Marie, P. L.: Compt. rend. Soc. de biol., 79:149, 1916.

5 Donnally, H. H.: J. Immunol., 19:15 (July), 1930.

6 Cohen, M. B., Ecker, E. E., Breitbart, J. R., and Rudolph, J. A.: J. Immunol., 18:419 (June), 1930.

7 Picado, C.: Compt. rend. Soc. de biol., 102:631 (Nov. 29), 1929.

8 Opie, E. L.: J. Immunol., 17:329 (Oct.), 1929.

9 Friedberger, E., Bock, G., and Fürstenheim, A.: Ztschr. f. Immunitätsforsch, 64:294, 1930.

10 Dooley, Parker: Serum Disease, J. A. M. A., 99:1778 (Nov. 19), 1932.

11 The recent California death was seemingly due to improper technical procedures, the injected serum containing a highly virulent strain of Staphylococcus hemolyticus. To obviate this danger, all California laboratories are now under effective control of the State Board of Health.

1 Dolley, P.: J. A. M. A., 99:1778 (Nov. 19), 1932.

2 Marie, P. L.: Compt. rend. Soc. de Biol., 79:149, 1916.

3 Little, R. B.: J. Immunol., 17:377, 1929.

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5 Picado, C.: Compt. rend. Soc. de Biol., 102:631, 1929.

6 Coca, A. F.: J. Immunol., 19:405, 1930. Donnally, H. H.: J. Immunol., 19:15, 1930.

7 Cohen, M. B., Ecker, E. E. Breitbart, J. R., and Rudolph, J. A.: J. Immunol., 18:419, 1930.

8 Mudd, S.: J. Immunol., 23:423, 1932.

after the alien protein injection.[9] By quantitative precipitin tests, measurable amounts of undenatured horse proteins can still be demonstrated in the donor as late as ninety days after intravenous injection.[10]

The possibility of "reversed anaphylaxis" in serum therapy[11] has only recently been taken into account in laboratory research. This is the possibility of producing typical anaphylactic reactions, in laboratory animals whose blood (or local tissues) contain certain specific antigen, by the subcutaneous, intraperitoneal or intravenous injection of homologous specific "immune" serum. The fact that many normal adults have bloods containing hereditary or acquired specific or heterophile antibodies[4] against microbic infections (*e. g.*, tuberculosis) that may be present in children suggests that "reversed anaphylaxis" is of more than academic interest.

While normal adult human serum is presumably the least toxic therapeutic agent that can be used for the passive immunization of man, the prevailing belief that its use is without clinical danger is not in accord with theoretical expectations. According to Netter's very scanty data,[12] serious serum disease should be expected in about three per cent of the cases.

In 1930, the term *autoanafilassi* appeared in Italian medical literature[13] as a descriptive title for this form of therapeutic shock. The suggested term *iso-anaphylaxis,* however, is more nearly in accord with American usage.

Stanford University.

W. H. MANWARING,
Palo Alto.

9 Manwaring, W. H., Marino, H. D., McCleave, T. C., and Boone, T. H.: Jour. Immunol., 13:357, 1927; 15:109, 1928.

10 Sox., H. C., Azevedo, J. L., and Manwaring, W. H.: J. Immunol., 21:409, 1931.

11 Opie, E. L.: J. Immunol., 17:329, 1929.

12 Netter, A.: Compt. rend. Soc. de Biol., 78:505, 1915.

13 Nelli, A. R.: Rinasc. med., 7:523, 1930.

HEMOPHILIA

Hemophilia has usually given disappointing results to treatment. Although called "bleeders' disease," paradoxically it is characterized by a normal bleeding time, but on greatly prolonged clotting time. The primary fault is thought to lie in physiologically defective platelets which fail to liberate adequate cephalin. If hemophilic blood be centrifuged, and the serum decanted and ground with a mortar and pestle, stained smears show that many of the platelets are broken up. If the serum be added, then, to the hemophilic red blood cells and mixed thoroughly, the blood clots in a short time. Apparently the blood platelets contain normal cephalin which merely needs liberation.

The work of Birch[1] has stimulated interest in the treatment by the use of the ovarian hormones. Since women are immune, it was postulated that they were protected by ovarian secretion, which broke up the resistant platelets. By giving ovarian extract parenterally, this worker obtained good clinical results in nine patients, less marked improvement in nine others, and a failure in one more. Generally, there occurred an increase in weight, hemoglobin, and vitality. Specifically, there was a decrease in number and severity of the hemorrhages and lowering of the coagulation time.

Since then there have been a number of clinical case reports of cessation of bleeding following administration of ovarian extract, but these are of inconclusive import because they were aided by transfusions, and in some the blood clotting time was not determined before treatment.

Accurate evaluation of therapy based even upon the response of the clotting time alone is impossible because of the extreme fluctuation in the untreated case. Birch reports one patient's clotting time as varying from forty minutes to five hours over a period of eighteen months.

Birch's theory hinges upon the presence in the normal male of a certain amount of female sex hormone which insures normal platelet action. "The normal male is not pure male, but part female." Dohrn,[2] Laqueur,[3] and others, have reported the presence of estrogenic substances in the urine of normal males. Birch's normal male controls showed the presence of the hormone in the urine. She reasoned that the hemophiliac lacked this protective hormone, and demonstrated to her satisfaction the absence of this hormone.

Other workers fail to agree with her. Frank[4] failed to find estrogenic substance in the urine of normal males in twelve instances. Freeman[5] could not find it in male urine before puberty, and in only one after puberty. Brem and Leopold[6] could not demonstrate any hormone in either a hemophiliac or a number of normal males. Clinically, in spite of daily injections of ovarian extract, for weeks they saw no improvement, either subjectively or in the reduction of the clotting time. Brown and Albright,[7] however, found estrogenic substance in the urine of a hemophilic patient before treatment with the sex hormone. The amount increased after treatment, but there was no coincident improvement in the clotting time.

This wide disparity in results certainly allows for no conclusions. It seems wise to hold judgment in abeyance until further evidence is assembled. Only careful study extending over a period of months and years can clarify the situation.

902 Wilshire Medical Building.

JOHN MARTIN ASKEY,
Los Angeles.

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